

UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 97-022-D1-CO)

PATENT

IN THE APPLICATION OF:

Rubin, *et al.*

Serial **10/685,737**

No.

Filed: **October 15, 2003**

Title **A System for Cell-Based Screening**

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Examiner: **Skibinsky, A. L.**

Group Art Unit: **1631**

Confirmation No.: **6145**

APPELLANTS' REPLY BRIEF

Dear Sir:

This Reply Brief is submitted pursuant 37 C.F.R. 41.41, within two months from the March 19, 2009 mailing of the Examiner's Answer which included a new ground of rejection. Applicants are filing this Reply Brief in order to respond to the new ground of rejection and in order to maintain the Appeal. If additional fees are due the Commissioner is authorized to charge our deposit account number 13-2490.

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I. Status of Claims

Claims 40-48 are pending in this application. Claims 40-48 are being appealed. Of these claims, claim 40 is independent.

Claims 40-48 were finally rejected in the Final Office Action mailed June 10, 2008. A Notice of Appeal was filed via EFS on November 10, 2008. The Appeal Brief was filed via EFS on December 4, 2008, within two months of the filing of the Notice of Appeal. An Examiner's Answer was mailed March 19, 2009 and contained a New Ground of Rejection of claims 40-48. The Reply Brief is being filed within two months of the mailing of the Examiner's Answer.

II. Grounds of Rejection to be Reviewed on Appeal

1. Whether claim 40-48 are unpatentable under 35 U.S.C. § 101
2. Whether claims 40-42 and 44-48 are unpatentable under 35 U.S.C. § 103(a) over Marks et al, in view of Kallal et al in further view of Proffitt et al.
3. Whether claim 43 is unpatentable under 35 U.S.C. § 103(a) over Marks et al, in view of Kallal et al in further view of Proffitt et al as applied to claims 40-42 and further in view of Dunlay, et al.

III. Argument

There are now three pending rejections, one newly issued rejection and the previous two remaining rejections of claims 40-48. Claims 40-48 are rejected as directed to non-statutory subject matter. Claims 40-42 and 44-48 are rejected under Marks et al, in view of Kallal et al in further view of Proffitt et al. Claim 43 is rejected under 35 U.S.C. § 103(a) as obvious over Marks et al, in view of Kallal et al in further view of Proffitt et al as applied to claims 40-42 and further in view of Dunlay, et al..

With reference to the rejection under 35 U.S.C. § 101, Applicants hereby state on the record that that the machine readable storage medium of the instant claims do not encompass non-physical embodiments and thus do not encompass non-statutory subject matter. With reference to the rejections under 35 U.S.C. § 103(a), Applicants respectfully assert that the Patent Office's rejection does not meet the statutory standard required for

an obviousness rejection under 35 U.S.C. §103(a). The reasons supporting patentability are set forth below.

A. Response to the New Ground of Rejection of Claims 40-48 as being directed to non statutory subject matter

Claims 40-48 have been newly rejected as being directed to non-statutory subject matter. For the following reasons, the Applicants have overcome the newly applied rejection.

i. Applicants do not intend to cover non-physical embodiments of machine readable storage medium.

Applicants were informed during an Examiner Interview (which included two Supervisors) regarding a similar 101 rejection for a different case, which also recited a “machine readable storage medium,” that a clear statement on the record was required in order to overcome the instant rejection. Thus, Applicants state, on the record, that the machine readable storage medium of the instant claims do not encompass non-physical embodiments and thus do not encompass non-statutory subject matter. Thus, based upon the above statement, Applicants respectfully request reconsideration and withdrawal of the rejection.

B. The Office Erred in Rejecting Claims 40-42 and 44-48 under 35 U.S.C. § 103(a) as being obvious over Marks, et al, in view of Kallal, et al in further view of Proffitt, et al.

Claims 40-42 and 44-48 stand rejected as obvious over Marks, et al, in view of Kallal, et al in further view of Proffitt, et al. For the following reasons, the Applicants respectfully traverse.

i. The cited references alone or in combination do not teach or disclose all of the claim limitations

In order to establish a *prima facie* case of obviousness the Patent office must establish that the prior art references alone or in combination must teach or suggest *all* the claim limitations. MPEP § 706.02(j).

The references alone or in combination do not teach, suggest, or make obvious all of the claim limitations of presently pending claim 40.

Presently pending claim 40 recites as follows:

A machine readable storage medium comprising a program containing a set of instructions for causing a cell screening system to execute procedures for measuring internalization of cell surface receptor proteins in individual cells on an array of locations which contain multiple cells, wherein the procedures comprise:

- a) identifying internalized cell surface receptor proteins in multiple individual cells on the array of locations, wherein the individual cells comprise at least a first luminescent reporter molecule that labels a cell surface receptor protein of interest resulting in a labeled cell surface receptor protein, and at least a second luminescent reporter molecule that reports on cells, wherein the identifying comprises determining whether luminescent signals from the labeled cell surface receptor protein in the individual cells identified by the at least second luminescent reporter molecule meet or surpass a user-defined threshold luminescent intensity, wherein luminescent signals from the labeled cell surface receptor protein that meet or surpass the user-defined threshold luminescent intensity represent an internalized cell surface receptor protein;
- b) **calculating a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein wherein the calculations provide a measure of internalization of the cell surface receptor protein in the individual cells; and**
- c) displaying data on the measure of internalization of the cell surface receptor protein in the individual cells.

As admitted by the Patent Office in the rejection mailed June 10, 2008, “Marks in view of Kallal et al. does **not** teach calculating a number and or percent of the individual cells that internalized the at least first luminescently labeled reporter molecule.” The Patent Office then asserts that Proffitt et al. cure this deficiency by teaching “a computerized scanning system and algorithm that is able to measure the relative cell numbers that contain a fluorescent label.” The Patent Office further states that in Proffitt et al, “[t]he total relative fluorescence intensity for the entire well containing cell is

determined...” While Proffitt is asserted to cure the deficiencies of Marks et al in view of Kallal et al. the Patent Office does not assert that Proffitt et al teach “calculating a number and or percent of the **individual cells** that internalized the at least first luminescently labeled reporter molecule,” but instead the Patent Office admits that Proffitt et al teach calculating the intensity of the “entire well” and measures “the relative cell number.” Thus, as admitted by the Patent Office, Proffitt et al does **not** actually teach the stated claim limitation, as Proffitt et al does **not** teach measuring fluorescence from individual cells, but rather teaches a homogeneous assay, in which the fluorescence from the entire well is measured and then adjusted to get a measurement of the relative cell numbers. Thus, Proffitt et al, in fact, does **not** cure the deficiencies of the other references.

The Patent Office goes on to assert in the Action mailed June 10, 2008 that:

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the procedure of labeling the internalizing receptor a [*sic*] fluorescent protein as taught by Marks in view of Kallal et al and then measuring the number of cells that had the internalized fluorescent protein with the computerized scanning system as taught by Proffitt et al. One of skill in the art would have been motivated to use the cell quantifying fluorescently labeled cells as taught by Proffitt et al to measure the internalization of cell surface receptors as taught by Marks in view of Kallal et al.

However, as argued above, Proffitt teaches looking at the total fluorescence of the collection of cells in the well and then determining relative cell number. Proffitt does not teach calculating a number and or percent of the **individual cells**. Thus, contrary to the Patent Office’s assertion, it would be impossible to “measure[ing] the number of cells that had the internalized fluorescent protein” using the methods of Proffitt, since Proffitt teaches looking at the total fluorescence of the collection of cells in the well.

Assuming that Marks in view of Kallal teaches labeling an internalizing receptor fluorescent protein, as asserted by the Patent Office, these labeled internalizing receptor proteins would fluoresce both when the receptor was localized to the plasma membrane and when it was internalized. Thus, using the measurement methods taught by Proffitt, which teaches looking at the total fluorescence of the collection of cells in the well, would result in an inability to distinguish between cells in which the receptor has

internalized and cells in which the receptor is localized to the cell surface. In both circumstances the cell would emit the fluorescence and the methods of Proffitt would simply look at total fluorescence from the well. Thus, given the methods of Proffitt, it is not possible to calculate **“a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein** as recited in the instant claims; and, as admitted by the Patent Office, Marks in view of Kallal does not teach this claim limitation either. Therefore, the combination of Marks in view of Kallal and further in view of Proffitt do not teach **“calculating a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein”**

The Examiner has responded to this argument in the Examiner’s Answer mailed March 19, 2009 by asserting that “Proffitt et al. teach the DIM-SCAN gives a linear proportion of relative fluorescence vs. that number of cells per well” and such measurements “teach calculating 1,000 cells/well and determining ‘excellent linearity’ with respect to fluorescence.” However, as noted previously and above, the methods taught by Proffitt, which teaches looking at the **total fluorescence** of the collection of cells in the well, would result in an inability to distinguish between cells in which the receptor has internalized and cells in which the receptor is localized to the cell surface. In both circumstances the cell would emit the fluorescence and the methods of Proffitt would simply look at **total fluorescence** from the cells in the well. Thus, given the methods of Proffitt, it is not possible to calculate **“a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein”** as recited in the instant claims. The Examiner has not provided any additional evidence that Proffitt et al teach “a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein, but has merely asserted that, based upon Proffitt et al., “it would be obvious for one of skill in the art to ‘calculate a number and/or percent of the individual cells’ based on the known values of relative fluorescence.” The pending claims do not just recite calculating “a number and/or percent of the individual cells” but go on to recite “a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein. The Examiner has not addressed the quoted claim in its entirety including all limitations, but has stopped short and only addressed the claim limitation up to “a number and/or percent of the individual cells.” The Examiner has

provided no evidence or support that Proffitt et al teaches calculating “a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein.” The Examiner hasn’t even asserted that Proffitt et al teaches calculating “a number and/or percent of the individual cells that internalized the labeled cell surface receptor protein.” Thus, the Examiner has provided no evidence or support that Proffitt teaches all of the claim limitations.

Thus, the combination of references cited by the Patent Office does not teach or suggest machine readable storage media for identifying internalized cell surface receptor proteins in multiple **individual cells** and calculating a number and/or percent of the **individual cells that internalized the labeled cell surface receptor protein** wherein the calculations provide a measure of internalization of the cell surface receptor protein in the **individual cells** and thus the Patent Office has not established a *prima facie* case of obviousness with respect to the invention of independent claim 40. Since the remaining claims all depend from claim 40, it is also clear that the Patent Office has not established a *prima facie* case of obviousness with respect to them.

Therefore, the Applicants respectfully request reconsideration and withdrawal of the rejection.

C. The Office Erred in Rejecting Claim 43 under 35 U.S.C. § 103(a) as being obvious over Marks, et al, in view of Kallal, et al in further view of Proffitt, et al. as applied to claims 40-42 and further in view of Dunlay, et al.

Claim 43 stands rejected as obvious over Marks, et al, in view of Kallal, et al in further view of Proffitt, et al as applied to claims 40-42 and further in view of Dunlay, et al. For the following reasons, the Applicants respectfully traverse.

i. The cited references alone or in combination do not teach or disclose all of the claim limitations

In order to establish a *prima facie* case of obviousness the Patent office must establish that the prior art references alone or in combination must teach or suggest *all* the claim limitations. MPEP § 706.02(j).

Claim 43 is dependent on claim 40 and thus shares all of the claim limitations of claim 40. Marks et al in view of Kallal et al in further view of Proffitt do not teach,

suggest or make obvious all of the claim limitations of claim 40 as outlined above in section A. The addition of Dunlay et al. does not cure the deficiencies of Marks et al, Kallal et al and Proffitt et al as applied to claim 40 and thus, the combination of all of the references does not teach suggest or make obvious the claim limitations of pending claim 40 or its dependent claim 43. Thus, it is clear that the Patent Office has not established a *prima facie* case of obviousness with respect to the invention of independent claim 40, nor the dependent claims, including claim 43. Therefore, the Applicants respectfully request reconsideration and withdrawal of the rejection.

C. Conclusion

In summary, Applicants have stated on the record that the machine readable storage medium of the instant invention does not include non-physical embodiments and thus does not include non-statutory subject matter, thereby obviating the newly applied rejection under 35 U.S.C. § 101. Furthermore, the presently claimed methods cannot be rendered obvious by Marks, et al, in view of Kallal, et al in further view of Proffitt and further in view of Dunlay et al because Marks, et al alone or in combination with all of the further references does not teach all the elements of the presently pending claims. The combination of Mason et al. in view of Kallal et al and Proffitt et al provides no teaching or suggestion regarding methods or machine readable storage media for identifying internalized cell surface receptor proteins in multiple **individual cells** and calculating a number and/or percent of the **individual cells that internalized the labeled cell surface receptor protein** wherein the calculations provide a measure of internalization of the cell surface receptor protein in the **individual cells**. Accordingly, the Applicants respectfully submit that this rejection is improper.

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Respectfully Submitted,

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